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CLAIMS 20-22 AND 36

Applicant notes that claims 20-22 and 36, pending herein, were not included in the Restriction Requirement.

Claims 20-22 are dependent on claims 17 and 18, and therefore should be included in Group III, as the Requirement is currently drawn.

Claim 36 is dependent on claim 32, and therefore should be included in Group IV, as the Requirement is currently drawn.

Applicant respectfully requests that the Examiner make the above corrections to the Requirement.

TRAVERSAL OF RESTRICTION REQUIREMENT

Applicant respectfully traverses the Restriction Requirement as between Groups I and IV, and as between Groups II and III. This application is the U.S. national stage of International Patent Application No. PCT/US97/06509, in accordance with 35 U.S.C. §371. As stated in MPEP 201, national stage applications of international applications are similar to national applications, but there are differences. Among these differences is inapplicability of restriction practice to national stage applications. Restriction practice is applied to national applications, but unity of invention practice is applied to national stage applications (see, MPEP 201 and MPEP 1893.03(d)).

Lack of Unity Standard

When the U.S. Patent Office considers an international application **during the national stage**, restriction must be based on unity of invention, which is governed by PCT Rule 13 (see MPEP 1893.03(d); Caterpillar Tractor Co. v. Commissioner of Patents and Trademark, 650 F. Supp. 218, 31 USPQ 590 (E.D. Virginia, 1986); In re Caterpillar Tractor Co., 228 USPQ 77). In the Caterpillar cases it was ultimately held that the language in Rule 13.1 "specially adapted" is not to be interpreted as meaning that the process of manufacture can only be used to manufacture the product because this interpretation is in conflict with the PCT Rule, which provides that no national law shall require

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compliance with requirements relating to the form or contents of the international application different from or additional to those which are provided in the Treaty (Article 27 of the PCT). Thus, the U.S. Patent Office cannot impose requirements that differ from those provided in the Treaty. Since restriction practice differs from and is more restrictive than unity of invention, the unity of invention rules must govern.

Therefore, it is respectfully submitted, and it appears that the Office has acknowledged, that the rules of unity of invention (PCT Rule 13.1 and 37 C.F.R. §1.475) apply to this application. Rule 13.1 requires that an international application shall relate to one invention only or to a **group of inventions so linked as to form a single general inventive concept.**

Carell et al.

In this instance, it is respectfully submitted that the products and processes of Groups I and IV, and of Groups II and III, form a group of inventions so linked as to form a single general inventive concept, as described in detail below. Briefly, Groups I and IV, and Groups II and III, are directed to products and processes for the manufacture of the products. The Office Action urges that Carell et al. (1994) Angew. Chem. Int. Ed. Eng. 33(20):2059-2061 anticipates the special technical feature of Group I and thereby destroys unity of invention. Applicant respectfully disagrees.

The claims of instant Group I

Instant claim 1 is directed to a process for generating a combinatorial set of molecules of core structure M, involving (a) preparing a plurality of immobilized molecules of core structure M, where the molecules contain a plurality of reactive moieties, each reactive moiety being blocked by a blocking group, where at least three of the blocking groups are independently removable under at least three different conditions, and (b) removing certain blocking groups and derivatizing the resulting reactive moieties in a preprogrammed, regioselective manner, where each member of a combinatorial set is uniquely

derivatized at at least one reactive moiety with a unique substituent, thereby generating a combinatorial set of molecules of core structure M.

Instant claim 3 defines the immobilized molecule as a multifunctional, low molecular weight compound of the general formula MD_n . Claim 4 further defines the low molecular weight compound as a saccharide, aminosugar, deoxysugar, nucleoside, nucleotide, coenzyme, amino acid, lipid, steroid, vitamin, hormone, alkaloid or small molecule drug compound.

Instant claim 11 defines the reactive moieties as OH, SH, NH_2 , CO_2H , SOH, SO_2H , SO_3H , CHO, keto, phosphate, phosphite, phosphoramidite, halogen, CN, CNS, NCS, NCO and derivatives thereof.

Instant claims 12-16 specify that the immobilized molecules are based on a linkage to a solid support, and also define the linkages and the solid supports.

Thus, the instant claims of Group I are directed to processes for combinatorial synthesis based on immobilized molecules of core structure M, where the immobilized molecules contain a plurality of blocked reactive moieties. At least three of the blocking groups must be orthogonal. Certain of the blocked reactive moieties are unblocked and derivatized in a preprogrammed, regioselective manner.

Disclosure of Carell *et al.* and differences from the claims of instant Group I

Carell *et al.* disclose synthesis of libraries containing small organic molecules in solution (see, page 2059, second full paragraph, first sentence). The core molecules, xanthenes and cubanes, contain acyl chlorides that are reacted in a random method with amines, including small heterocyclic amines and amino acids.

The cited reference does not disclose a process for combinatorial synthesis based on immobilized molecules of core structure M, as required by the claims of instant Group I. The reference discloses solution combinatorial synthetic methods. Nor does the reference disclose immobilized molecules that contain a plurality of blocked reactive moieties for use in the process disclosed

therein, as required by the instant claims. The xanthene and cubane molecules for use in the combinatorial synthetic methods of Carell *et al.* possess acyl chloride groups, not blocked reactive moieties, as required by the instant claims.

Furthermore, the cited reference does not disclose selective removal of certain blocking groups and derivatization of the resulting reactive moieties in a preprogrammed, regioselective manner to produce a combinatorial set of compounds of core structure M. Carell *et al.* disclose reaction of the acyl chloride groups in a random manner to produce combinatorial libraries.

Therefore, the disclosure of Carell *et al.* does not anticipate the claims of instant Group I. Unity of invention does exist as between Groups I and IV, and withdrawal of the lack of unity rejection is respectfully requested.

PCT Rule 13

Furthermore, it is respectfully submitted that Groups I and IV, and Groups II and III, relate to a product and a process for the manufacture of said product, and therefore do not lack unity of invention under PCT Rule 13.

Groups I and IV

Groups I and IV are directed to a process for generating a combinatorial set of molecules of core structure M, and a combinatorial set of compounds with core structure M, respectively. Such groups of claims do not lack unity of invention under PCT Rules 13.1 and 13.2. See 37 CFR §1.475(b):

An international or a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:

- (1) A product and a process specially adapted for the manufacture of said product...

The claims of Group IV are directed to a product (a combinatorial set of compounds with core structure M), and the claims of Group I are directed to a process for the manufacture of the product (a process for generating a

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combinatorial set of molecules of core structure M). Such Groups of claims do not lack unity of invention, and therefore should be examined in one application.

Applicant respectfully requests reconsideration of the lack of unity objection as between Groups I and IV. In view of Applicant's election of Group I herein, it is respectfully requested that the claims of Groups I and IV, i.e., claims 1, 3, 4, 11-16 and 23-36, be examined in the instant application.

Groups II and III

Groups II and III are directed to a process for generating a combinatorial set of oligomers, and a composition comprising an oligonucleotide (an oligomer), respectively. Such groups of claims do not lack unity of invention under PCT Rules 13.1 and 13.2. See 37 CFR §1.475(b):

An international or a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:

- (1) A product and a process specially adapted for the manufacture of said product...

The claims of Group III are directed to a product (a composition comprising an oligonucleotide, an oligomer), and the claims of Group II are directed to a process for the manufacture of the product (a process for generating a combinatorial set of oligomers). Such Groups of claims do not lack unity of invention, and therefore should be examined in one application.

Applicant respectfully requests reconsideration of the lack of unity objection as between Groups II and III. It is respectfully requested that the claims of Groups II and III, i.e., claims 2 and 5-22, be combined in the instant application. Applicant has elected Group I herein. Applicant reserves the right to file divisional application(s) directed to the subject matter of the non-elected claims.

TRAVERSAL OF REQUIREMENT FOR ELECTION OF SPECIES

Applicant respectfully traverses the Requirement for Election of Species. It is respectfully submitted that, as described in detail below, the species are so linked as to form a single general inventive concept within the meaning of PCT Rule 13.1 (see, MPEP 1893.03(d)). Furthermore, it is respectfully submitted that the requirement for election of a single species is inconsistent with the subject matter of the instant claims.

Election of Species in Group IV

First, it is noted that the Office Action lists, for Group III on pages 4 and 5, the requirements (a) through (h) (see, the last 8 lines of page 4 and the first two lines of page 5). Since requirements (e) through (h) relate to species of claims 24, 26, 27 and 31, and these claims are within Group IV, it is assumed herein that if Applicant had elected Group IV, a further election of a single species from each of claims 24, 26, 27 and 31 would have been required. It is further assumed that if Applicant had elected Group III, a further election of species as set forth in (a) through (d) would have been required.

Applicant respectfully requests clarification from the Examiner in this regard.

Unity of Invention

As noted in detail above, this application is the U.S. national stage of International Patent Application No. PCT/US97/06509. Therefore, PCT regulations with respect to unity of invention are applicable herein (see, PCT Rule 13, 37 CFR §1.475, and MPEP 1893.03(d)). Unity of invention is based on the basic principle that an applicant has the right to include in a single application those inventions (e.g., species) which are so linked as to form a single general inventive concept (MPEP 1893.03(d)). Applicant respectfully submits that, given the subject matter of the instant claims, the building blocks (e.g., nucleosides), reactive groups, and protecting groups are so linked as to

forma single general inventive concept. Therefore, a requirement to elect a single species in each of these elements is inappropriate.

The instant claims are directed to a combinatorial protecting group strategy for multifunctional molecules. In particular, the claims are directed to products and processes for oligonucleotide synthesis and for preparation of combinatorial libraries. Restriction of the claims to the single species required in the Office Action would negate a fundamental aspect of the subject matter of the instant claims (*i.e.*, the combinatorial aspect).

Restriction of Monomers

The instant claims are directed to products and processes for preparation of the products, where the products are a combinatorial set of molecules of core structure M, or a composition comprising an oligomer. In particular, the claims are directed to (1) oligomers comprising not only of one moiety, but in the case of oligonucleotides, of at least all four of the natural building blocks, and (2) within the oligomer, using different protecting groups at different positions within the oligomer chain (even at the same type of building block).

As described in detail in the application, such products are useful as drugs. Modified oligonucleotides are used in an antisense/triplex DNA approach. Modifications are necessary to provide oligonucleotides of desired cell and nuclear transport properties, while retaining the desired activity. The instant processes provide such various products in a preprogrammed, specific manner requiring only one oligonucleotide synthesis run. In order to fully utilize the products and processes of the instant claims, use of various monomers is required.

Therefore, restriction of the claims to only a single building block, particularly where the products are oligonucleotides, (*e.g.*, a single disclosed species from claim 10; a single disclosed species representing B or B^{R2A} or B^{R2B}; or a single disclosed species from claim 31) is not appropriate since these building blocks are all part of a single general inventive concept. The claims are

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directed to compositions and combinatorial libraries containing oligonucleotides, and processes for preparation of same. If Applicant were required to elect a single disclosed nucleoside species as required, then the search, and any resulting allowed claims, would be limited to oligonucleotides containing only the single elected nucleoside (i.e., TTTTTTT..., GGGGGG..., AAAAAA..., CCCCCC..., etc.). Such a requirement is inconsistent with the subject matter of the instant claims, and violates Applicant's right to have all species that form a single general inventive concept included in a single application.

Restriction of Reactive Groups and Protecting Groups

Furthermore, the application is directed to a combinatorial protecting group strategy for multifunctional molecules. Restriction to a single reactive group or a single protecting group is inconsistent with the subject matter of the instant claims.

Restriction of the claims to only a single reactive group, e.g., a reactive group of claims 11 or 24, is not appropriate because the claims are directed to products and processes that have different protecting groups at different positions (i.e., on different reactive groups) within the product. To restrict the reactive groups to a single reactive group would negate a fundamental aspect of the instant claims. The different reactive groups are part of the single general inventive concept of the instant claims.

Restriction of the claims to only a single protecting group, e.g., a single R^{4A} or R^{4B} group; or a single R^{2A} or R^{2B} group; or a single group for R^3 ; is also not appropriate because the claims are directed to different protecting groups at different positions within the product. To restrict the reactive groups to a single reactive group would negate a fundamental aspect of the instant claims. The different protecting groups are part of the single general inventive concept of the instant claims.

Therefore, requiring election of a single disclosed reactive group or protecting group is inconsistent with the subject matter of the instant claims.

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Moreover, such requirement violates Applicant's right to have all species that form a single general inventive concept included in a single application (see, MPEP 1893.03(d)).

Summary

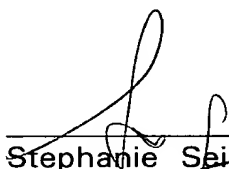
For the reasons given above, Applicant respectfully requests reconsideration and removal of the lack of unity objection as between Groups I and IV, and as between Groups II and III. Furthermore, Applicant respectfully requests reconsideration and removal of the lack of unity objection as relating to the requirement for election of a single species.

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In view of the above, examination of the application on the merits is respectfully requested.

Respectfully submitted,
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